Renal Replacement Therapy I: Indications and Timing

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Acute renal failure (ARF) is defined broadly as the abrupt loss of renal function that results in the failure of the kidney to excrete metabolic waste products, such as urea, or to maintain fluid and electrolyte homeostasis. The direct consequences of ARF are variable, and most often are characterized by volume overload, metabolic acidosis, hyperkalemia, hypo- or hypernatremia, and the accumulation of nitrogenous waste products in the blood. Although there have been substantial advances in our understanding of its pathogenesis, clinical advances in the treatment of ARF have been limited. Multiple pharmacologic interventions showed promise in animal models of ARF; however, no agents have proven to be effective in the clinical setting (see the article by Venkataraman elsewhere in this issue). As a result, the management of ARF remains primarily supportive; renal replacement therapy (RRT) serves as the cornerstone of treatment in patients who have persistent severe acute renal dysfunction.

The use of hemodialysis in ARF entered clinical practice in the decade following World War II [1–6]. In its initial application, hemodialysis was applied to patients who had advanced symptoms of renal failure, including clinical uremia, severe hyperkalemia, and pulmonary edema [1,6,7]. Although acute volume overload, electrolyte disturbances, and uremia could be reversed, a clear reduction in mortality could not be demonstrated, with high complication rates as a result of wasting, anemia, sepsis, and delayed wound healing [7]. In the period
following the Korean conflict, Paul Teschan and colleagues [7] from the United States Army Medical Corps introduced the concept of “prophylactic” dialysis, with initiation of treatment before the onset of overt symptoms. Writing in 1960, Teschan et al postulated that “…dialysis, applied before uremic symptoms appear, should prevent both the uremic syndrome and many of its commonly lethal sequelae.”

Despite the more than 4 decades that have passed since Teschan et al’s seminal article, mortality rates in ARF remain high—exceeding 50% in many studies—and many fundamental issues regarding the management of RRT remain unresolved [8–18]. Among these are the indications for, and timing of, initiation of RRT; the optimal dose and modality of therapy; the impact of bioincompatibility of the extracorporeal circuit on renal recovery and survival; and the timing of discontinuation of renal support. This article reviews the indications for RRT in ARF as well as the available data regarding optimal timing for initiation of therapy.

Indications for renal replacement therapy in acute renal failure

As in chronic kidney disease, overt disturbances of extracellular volume and body fluid composition remain the objective indications for initiation of RRT in ARF (Box 1). These include volume overload, hyperkalemia, severe metabolic acidosis, and overt uremic symptoms. The presence of progressive azotemia also is regarded as an indication for renal support, although a specific threshold for the severity of azotemia is debated (see later discussion) The modulation of inflammatory mediators, particularly in patients in whom ARF occurs in the setting of sepsis or multi-system organ failure, has been proposed as an additional indication for RRT, but must be considered experimental [19].

Volume overload

Volume overload generally is recognized as an indication for RRT in ARF. All modalities of RRT are effective at diminishing intravascular volume. Subjective criteria for initiation of therapy include impairment of cardiopulmonary function.

<table>
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<th>Box 1. Indications for renal replacement therapy in acute renal failure</th>
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<td>Volume overload</td>
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<td>Hyperkalemia</td>
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<td>Metabolic acidosis</td>
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<td>Uremic signs or symptoms</td>
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<td>Progressive azotemia in the absence of uremia</td>
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by pulmonary vascular congestion or compromise of cutaneous integrity or wound healing by peripheral edema. Although these conditions may correlate with changes in central venous, pulmonary artery and pulmonary capillary occlusion pressures, and arterial oxygen saturation, specific objective criteria for initiation of renal support are not defined.

The appropriateness of a trial of diuretic therapy before initiation of renal support also has been questioned. Mehta and colleagues [20] performed a retrospective analysis of data from 522 critically ill patients who had ARF. Fifty-nine percent of these patients had been treated with diuretics. After adjustment for relevant covariates and the propensity for diuretic use, they observed a significant increase in the risk of death or nonrecovery of renal function (odds ratio [OR], 1.77; 95% confidence interval [CI], 1.14–2.76). On the basis of this, they concluded that diuretic therapy was potentially deleterious in patients who had ARF. They noted, however, that the increased risk was borne largely by patients who were unresponsive to diuretics; this suggested that this increased risk might reflect selection for a more severe degree of renal injury. Uchino et al [21] conducted a similar analysis using a database of 1743 critically ill patients at 54 centers in 23 countries. Using a similar propensity-adjusted mortality model, these investigators found an OR for mortality associated with diuretic use of only 1.21 (95% CI, 0.96–1.50; \( P = .10 \)). Similar results were obtained using an alternative propensity-adjusted mortality model and using a multi-collinearity–adjusted model. Thus, the risk associated with diuretic therapy that was observed by Mehta et al could not be confirmed in this large multi-national cohort. In addition, a recent, randomized controlled trial of high-dose furosemide in ARF did not demonstrate any increase in mortality associated with diuretic therapy as compared with placebo [22]. A trial of diuretic therapy in volume-overloaded patients is not unreasonable before the initiation of RRT. If, however, there is minimal or no response to 160 mg of furosemide, or an equivalent dose of other loop-acting diuretics, further diuretic therapy is not warranted.

Hyperkalemia

Treatment of hyperkalemia with evidence of myocardial toxicity was one of the early indications for hemodialysis in ARF. Hyperkalemia is a well-recognized complication of ARF, which, if not treated, may be rapidly fatal. Most medical therapies for hyperkalemia (eg, intravenous calcium to directly antagonize the effects of hyperkalemia on the myocardial cell membrane, intravenous insulin and intravenous or inhaled \( \beta \)-adrenergic agonists to shift potassium into the intracellular compartment) primarily are temporizing measures. Three modalities are available to decrease total body potassium burden: diuretic therapy, enteric potassium-binding resins, and dialysis. In patients who have severe renal failure, diuretic therapy generally is ineffective in promoting kaliuresis. Although sodium polystyrene sulfonate can enhance fecal potassium losses, its use is limited in patients with recent intra-abdominal or gastrointestinal surgery, ileus, or bowel ischemia. Dialysis provides the most rapid means of decreasing the serum
potassium concentration; however, because of variability in study design and evolution of dialysis techniques, it is difficult to determine the expected potassium removal during a single dialysis treatment [23]. Studies that used hollow fiber cuprophan hemodialysis membranes and blood flows of only 200 mL/h demonstrated removal of between 50 and 80 mmol of potassium during a 4-hour treatment [24]. In these studies, serum potassium levels decreased by more than 2 mmol/L; however, postdialysis rebound as potassium redistributes out of the intracellular compartment is frequent. Even greater clearances of potassium may be achieved by using more permeable synthetic hemodialysis membranes and greater blood flow rates; however, the rate of potassium removal ultimately is limited by the rapid decrease in the concentration gradient between plasma and dialysate [24]. The rates of potassium removal by peritoneal dialysis and continuous RRT are substantially less than that achieved during hemodialysis; however, the longer duration of therapy provides satisfactory control of hyperkalemia over time and mitigates the postdialysis potassium rebound.

As with volume status, a specific threshold level of serum potassium cannot be established as an indication of initiation of RRT. Myocardial toxicity from hyperkalemia is uncommon when the serum potassium concentration is less than 6.5 mmol/L [23]. Therefore, decisions regarding the initiation of treatment for control of hyperkalemia must take into consideration the absolute level and rate of increase of serum potassium, the patient’s overall condition, and the likely efficacy of medical therapy.

Metabolic acidosis

The role of alkali therapy in the treatment of metabolic acidosis, particularly lactic acidosis, is controversial [25,26] (see also the article by Kellum elsewhere in this issue). The use of RRT as an alternative to alkali replacement in metabolic acidosis can avoid some of the deleterious effects that are ascribed to aggressive alkali replacement, specifically volume overload and hypernatremia. Although progressive metabolic acidosis is a generally accepted indication for RRT, clinical trials to establish a threshold blood pH or serum bicarbonate concentration or to demonstrate improved patient outcomes have not been performed.

Other electrolyte disturbances

RRT may be used for the treatment of a variety of other electrolyte disturbances that can occur in the setting of ARF. These include severe hypo- and hypernatremia, hyperphosphatemia, hypo- and hypercalcemia, and hypermagnesemia. In the treatment of hyponatremia, caution must be used to ensure that rapid correction does not predispose to the development of the osmotic demyelination syndrome. A rapid decrease of serum phosphate and uric acid levels and control of acidemia using RRT is necessary in patients who have the tumor lysis syndrome to accelerate recovery of renal function.
Uremic signs and symptoms

The development of overt uremic signs or symptoms represent an obvious indication for initiation of RRT in ARF. Early manifestations of uremia, such as anorexia, nausea and vomiting, and pruritus, are nonspecific and may be difficult to differentiate from other comorbid conditions in patients who have critical illness. Mental status changes, which may represent uremic encephalopathy, also may be difficult to differentiate from other etiologies of delirium in the critically ill patient. Uremic pericarditis usually is a late complication, but requires urgent initiation of renal support given the high risk of intrapericardial hemorrhage and tamponade. As was emphasized more than 4 decades ago by Teschan et al [7], optimally, RRT should be initiated before the onset of overt uremic manifestations.

Azotemia in the absence of uremic signs and symptoms

In many patients, the sole indication for initiation of RRT in ARF is the presence of progressive azotemia in the absence of uremia or other indications for renal support. There is no consensus, however, on the degree of azotemia that warrants initiation of therapy (vide infra). In a multi-center trial that evaluated the dosing strategies for RRT in critically ill patients who had ARF, we observed substantial variation in practice regarding the degree of azotemia that was deemed appropriate for initiation of treatment between practitioners within individual institutions and between institutions (unpublished data).

Timing of initiation of renal replacement therapy

Beginning with the studies by Paul Teschan and colleagues [7] in the years following the Korean conflict, numerous studies have attempted to define the criteria for timing of initiation of RRT in ARF. These studies attempted to determine the balance between three major competing risks—the inherent risk that results from delay in therapy; the potential risk of harm as the result of RRT, including complications of therapy and the potential that dialysis may prolong the course of ARF; and the risk that early initiation of therapy will result in patients undergoing treatment who, if managed conservatively, might recover renal function without requiring RRT.

In their landmark report, Teschan et al [7] described a prospective, uncontrolled series of 15 patients who had oliguric ARF who were treated with “prophylactic” hemodialysis, defined as the initiation of dialysis before the serum urea nitrogen reached 100 mg/dL [7]. Patients received daily dialysis (average duration 6 hours) using twin-coil cellulosic dialyzers at a blood flow of 75 mL/min to 250 mL/min to maintain a predialysis serum urea nitrogen of less than 75 mg/dL. Caloric and protein intake were unrestricted. All-cause mortality
was 33%; mortality due to hemorrhage or sepsis was 20%. Although no control group was studied, the investigators reported that the results contrasted dramatically with their own past experience in patients in whom dialysis was not initiated until “conventional” indications were present. In a series of 45 patients who had ARF, Easterling and Forland [27] reported similar results. Although they lacked a control group, and therefore, were unable to draw any conclusions regarding improved survival with early dialysis, they also concluded that the prevention of uremic symptoms in ARF was desirable.

Between 1961 and 1972, three retrospective studies were published that compared outcomes between early and late initiation of dialysis in ARF (Table 1). Parsons et al [28] retrospectively analyzed 33 patients who had postoperative ARF who were treated with hemodialysis during the periods 1956 to 1958 and 1959. Survival in patients who were initiated on dialysis “early” (serum urea nitrogen between 120–150 mg/dL) was 75% as compared with 12% in patients in whom dialysis was initiated “late” (serum urea nitrogen >200 mg/dL). Fischer et al [29] described 162 patients who required hemodialysis between 1950 and 1964. Patients in whom dialysis was initiated when the serum urea nitrogen reached 150 mg/dL or when clinical deterioration was first observed had a 57% mortality rate as compared with 74% in patients in whom dialysis was not initiated until the serum urea nitrogen was greater than 200 mg/dL. Kleinknecht et al [30] described a series of 500 patients who had ARF who required dialysis during the period from 1966 to 1970. All patients were maintained on similar caloric (30 kcal/kg/d) and protein (1 g/kg/d) intake. Patients who received “prophylactic” dialysis (defined as early and frequent dialysis to maintain predialysis serum urea nitrogen less than 93 mg/dL) had a mortality rate of 27% as compared with 42% in patients in whom dialysis was initiated only if the serum urea nitrogen was greater than 163 mg/dL or if severe electrolyte disturbances were present. These investigators observed a marked reduction in mortality that was due to sepsis and gastrointestinal bleeding in the group that was dialyzed more aggressively.

Table 1
Studies of early versus late renal replacement therapy in acute renal failure

<table>
<thead>
<tr>
<th>Publication year</th>
<th>Design</th>
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<th>Serum urea nitrogen pre-RRT (mg/dL)</th>
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<td>Early 120–150</td>
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<td>Early &lt;90</td>
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<td>Early 71</td>
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The first prospective evaluation of “prophylactic” dialysis in ARF was reported by Conger [31] in 1975. In this study, 18 patients who had posttraumatic ARF that was sustained during the Vietnam War and were treated on the Naval Hospital Ship USS Sanctuary between April and October 1970 were assigned alternately to an intensive dialysis regimen to maintain the predialysis serum urea nitrogen and creatinine at less than 70 mg/dL and 5 mg/dL, respectively, or a nonintensive regimen in which dialysis was not performed until the serum urea nitrogen approached 150 mg/dL, the creatinine reached 10 mg/dL, or the patient developed clinical indications for dialysis (hyperkalemia, volume overload, or uremic encephalopathy). All dialysis treatments were provided using coil dialyzers. A minimum nutritional intake of 25 kcal/kg/d was provided as parenteral glucose; patients who were capable of oral feeding received a minimum of 0.75 g/kg/d of protein. Survival was 63% (5 of 8 patients) in the group that received intensive treatment as compared with 20% (2 of 10 patients) in the group that received nonintensive dialysis ($P < .01$). In addition, complications of hemorrhage (36% versus 60%) and gram-negative sepsis (50% versus 80%) were less frequent in the group that received intensive treatment.

Expanding on this study, Gillum et al [32] studied 34 patients who had ARF who were randomized to receive intensive hemodialysis (5 to 6 hours daily or every other day to maintain a predialysis serum urea nitrogen $< 60$ mg/dL and serum creatinine $< 5$ mg/dL) or nonintensive dialysis (5 hours daily to every third day, allowing the serum urea nitrogen to reach 100 mg/dL and the serum creatinine to reach 9 mg/dL). Patients were stratified based on etiology of ARF (trauma-surgery or medical) and were randomized in paired fashion when the serum creatinine reached 8 mg/dL. All patients were dialyzed using hollow fiber cellulose dialyzers. Although the mean ages of the patients in the two groups were similar, the age distribution was skewed in the group that received intensive dialysis, with clustering of the youngest ($< 40$ years) and oldest ($> 60$ years) patients. Protein intake was less in the group that was dialyzed intensively (0.55 ± 0.32 g/kg/d versus 0.77 ± 0.28 g/kg/d); however, the difference was not statistically significant. Mortality was greater in the group that was dialyzed intensively group (58.8% versus 47.1%), but given the small sample size, this was not statistically significant. Hemorrhagic and septic complications were more common in the group that was dialyzed nonintensively (hemorrhage: 24% versus 59%; sepsis: 47% versus 65%); however these differences also did not reach statistical significance. Based on these data, many practitioners adopted a threshold serum urea nitrogen of approximately 100 mg/dL for initiating RRT in ARF.

More recently, Gettings et al [33] reported the results of a retrospective analysis of early (serum urea nitrogen $< 60$ mg/dL) versus late (serum urea nitrogen $> 60$ mg/dL) initiation of continuous RRT (CRRT) in 100 adult patients who had posttraumatic ARF. The 41 patients who were “early” starters were younger (40.5 ± 17.9 years versus 48.0 ± 18.9 years; $P = .051$), but otherwise were comparable to the 58 “late” starters. Patients had similar Injury Severity Scores (early: 33.0 ± 13.5; late: 37.2 ± 15.0; $P = .178$) and Glasgow Coma Scale scores (early: 11.8 ± 3.8; late: 12.5 ± 3.7; $P = .349$) on admission. No other
index of severity of illness was reported. CRRT was initiated when the serum urea nitrogen was 42.6 mg/dL ± 12.9 mg/dL in the “early” group as compared with 94.5 mg/dL ± 28.3 mg/dL in the “late” group. Survival was 39% in the “early” group as compared with 20% in the late group.

Bouman et al [34] conducted a prospective, randomized trial that compared the early initiation of high-volume continuous venovenous hemofiltration (CVVH) (n = 35) with the early initiation of low-volume CVVH (n = 35) and the late initiation of low-volume hemofiltration (n = 26). The mean serum urea nitrogen in the two groups that received early initiation was 47 mg/dL as compared with 105 mg/dL in the group that received late initiation. Overall survival was 72.6% with no difference in survival between any of the three groups. Interpretation of these results must be tempered by the overall survival rate, which was much better than that reported in most studies of ARF suggesting differences in the study population, and by the small sample size studied.

Summary

Based on the current data it is not possible to draw firm conclusions regarding the appropriate timing of initiation of RRT in ARF. In 1960, Teschan et al wrote “While there is increasing recognition of the value of earlier dialysis, the published consensus, and the practice in many centers at present, is still to apply dialysis to relatively ill rather than to relatively healthy patients.”

Although our definition of early initiation of renal support has changed, definitive resolution of the appropriate timing for initiation of renal support in patients who have ARF requires a well-designed, adequately powered multicenter randomized trial.

References

[33] Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when